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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Patrick W. Rasche
Armstrong Teasdale LLP
One Metropolitan Square, Suite 2600
St. Louis, MO 63102

EXAMINER	
RAGHU, GANAPATHIRAM	
ART UNIT	PAPER NUMBER
1652	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/786,505	GROSS ET AL.	
	Examiner	Art Unit	
	Ganapathirama Raghu	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17,21-24,26 and 32-48* is/are pending in the application.

4a) Of the above claim(s) *6,10-15,21-24,26,32-36,38 and 39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 7-9, 16-17, 37 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Application Status

In response to the Office Action mailed on 08/37/2006, applicants' filed a response and amendment received on 02/07/2007. Said amendment, amended claims 1, 3, 7-9, 16-17, 37 and 40. Thus, Claims 1-17, 21-24, 26 and 32-48 are pending in the application. Claims 6, 10-15, 21-24, 26, 32-36, 38-39 and 41-48 remain withdrawn as they are drawn to non-elected inventions. Claims 1-5, 7-9, 16-17, 37 and 40 are now under consideration for examination.

Applicants' have also requested that the election/restriction be withdrawn. The Office in the letter dated 08/07/2006 clearly provided the reasons that the inventions are distinct and demonstrated that the inventions have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated was proper. The claims are drawn to different polynucleotides either encoding polypeptides of different sizes and structure as a result of alternative splicing or polynucleotides that correspond to transcription initiation sites and not encoding any polypeptide but correspond to transcription factor binding sites (promoter regions) and as such claims cover disparate subject matter and are distinct. Therefore, for the above cited reasons searching of all claims is a serious search burden and the request for reconsideration of the election/restriction requirement cannot be granted at this stage of the prosecution.

Objections and rejections not reiterated from the previous action are hereby withdrawn.

New-Matter/Objection to Specification

The amendment filed on 02/07/2007 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not

supported by the original disclosure is as follows: The three paragraphs added to the specification on 02-07-07 are new matter. Support has not been provided for the new paragraphs and none can be found. In particular the phrase "configured to generate transgenically generated phospholipase A2 (TGiPLA2) mice" cannot be found. The scope of nucleic acid sequences configured as claimed was not contemplated in the specification as originally filed.

Applicant is required to cancel the new matter in the reply to this Office Action.

New Matter-Claim Rejections 35 USC § 112

Claims 1, 7, 9, 37 and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 1, 7, 9, 37 and 40 are rejected because the phrase "configured to generate transgenically generated phospholipase A2 (TGiPLA2) mice" is new matter. The scope of nucleic acid sequences "configured" as claimed was not contemplated in the specification as originally filed. A "vector which can be used to generate a transgenic mouse" as in original claim 25 has a different scope than the nucleic acid sequences now claimed.

Claim Objections

Claims 1, 7, 9, 37 and 40 are objected to due to the following informality: Said claims recite "$iPLA_2$", this is not a standard abbreviation for phospholipase A_2 (PLA_2). The abbreviation should be expanded at least in the first recitation.

Claim 9 is objected to due to following informality: in line 2 of the claim, the phrase "sequence" should be inserted following "the antisense".

Amended claim 40 is objected to as Invitrogen is a trade name and therefore requires a superscript indicating Copyright or a trademark TM symbol.

Maintained-Claim Rejections: 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 and claims 2-5, 16-17 and 40 depending therefrom remain indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites the "....phrase phospholipase A2γ polypeptide...". What characteristics define or distinguish phospholipase A2γ from other phospholipase A2?. Clarification is required.

Applicants' have traversed this rejection with the arguments, "...phospholipsases A2 are a broad family of enzymes... accordingly reasons set forth above...rejections be withdrawn".

Applicants' arguments are not persuasive, because applicants' have not defined or distinguished phospholipase A2γ from other phospholipase A2.

Claim 7 and claim 8 depending therefrom remain as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 7 is rejected for the phrase "...has or modulates...", as the metes and bounds are not clear. It is not clear to the examiner the scope of the term "modulates" as to what the intended modulation is and compared to what? Clarification is required.

Applicants' have traversed this rejection with the arguments, "...modulates enzymic activity refers to a regulation of enzymic activity... accordingly reasons set forth above...rejections be withdrawn".

Applicants' arguments are not persuasive. First of all, it is not clear whether the polypeptide has both phospholipase A2γ activity and also auto-regulates its own activity or the said enzyme modulates the activity of other enzyme(s)? If so what are the targets, how is the said target modulated? Up-regulation or down-regulation? Finally, as the amended claims are directed to a vector configured and intended to generate transgenic mice expressing said polypeptides, what phenotype of transgenic mice is to be expected by one of ordinary skilled in the art? Clarification is required.

Claim 16 remains as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, because claim 16 is confusing, Must the reporter gene be a part of the vector? Examiner suggests inserting "said vector comprises" after "wherein" in line 2 and "which" after "reporter gene" in line 3. Correction is required.

Claim 37 remains as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 37 the inclusion of SEQ ID NO: 6 in parenthesis is confusing as it is unclear if what is within the parenthesis is a limitation of the claim or not. In the instant case it is assumed to not limit the claim to SEQ ID NO: 6. Clarification and correction is required.

Claim 40 remains as being indefinite because the phrase "a truncated $iPLA_2$..." is not clear.

Applicants' have traversed this rejection with the arguments, "...claim has been amended...rejections be withdrawn".

Applicants' arguments are not persuasive. First of all, it is not clear whether the truncated $iPLA_2$ polypeptide has any enzymic activity or not nor is it clear what sequence(s) are comprised in the truncated polypeptide. Finally, as the amended claims are directed to a vector configured and intended to generate transgenic mice expressing said polypeptides, what phenotype of transgenic mice is to be expected by one of ordinary skilled in the art? Clarification is required.

New-Claim Rejections 35 USC § 112

Amended claim 9 is rejected, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 9 recites the limitation "wherein the anti-sense is configured to generate transgenically generated phospholipase A_2 ($TiPLA_2$) mice". Clarification is required regarding use of anti-sense sequence to generate a transgenic mouse. Is it a "gene knock-in" or "gene knock-out" transgenic mice and what is the expected phenotype?

Amended claim 37 is rejected, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 37 recites the limitation "the full-length phospholipase A_2 ($iPLA_2$) coding sequence (SEQ ID NO: 6) " in the claim. There is insufficient antecedent basis for this limitation in the claim.

Amended claim 40 is rejected, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 40 recites the phrase "...SV40 promoter of Invitrogen...". There are many expression vectors from Invitrogen with SV40 promoter, without specific sequence identifying characteristics, one of ordinary skilled in the art would not be able to recognize which sequence is encompassed in the instant claim.

Maintained-Claim Rejections: 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 7-9, 16-17, 37 and 40 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 1-5, 7, 9, 16-17, 37 and 40 are directed to any polynucleotide encoding any phospholipase A2γ for use in making a transgenic mouse (as in claims 1-3, 16-17 and 40) or any polynucleotide encoding a phospholipase A2γ wherein the isolated polynucleotide sequence has at least 90% sequence identity to SEQ ID NO: 6 and encodes a polypeptide with phospholipase A2γ activity or capable of modulating any undefined enzymic activity for use in generating a transgenic mouse (as in claims 7-8) or any anti-sense sequence of SEQ ID NO: 6 in a vector configured and intended to generate a transgenic mice (as in claim 9) or a transgenic construct comprising the full-length phospholipaseA2 coding sequence for myocardial specific expression of transgenically generated

phospholipaseA2 in transgenic mouse (as in claim 37) or any truncated fragment of said polypeptide for use in making a transgenic mouse (as in claim 40), said construct further comprising a reporter gene (as in claims 16-17), host cell (as in claims 4-5) intended for overexpressing said polypeptide in a transgenic mouse.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

The art at the time of filing, taught the phenotype of transgenic animals was unpredictable. For example, one transgene could cause two different phenotypes in mice and rats. Mullins et al., (1990, Nature, Vol. 344, pg 541-544) produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse Ren-2 renin transgene. Hammer et al., (1990, Cell, Vol. 63, pg 1099-1112) describes spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human β_2-microglobulin transgenes. Both investigations were preceded by the failure to develop human disease-like symptoms in transgenic mice (Mullins et al., 1989, EMBO, Vol. 8, pg 4065-4072; Taurog et al., 1988, J. Immunol., Vol. 141, pg 4020-4023) expressing the same transgenes that successfully caused the desired symptoms in transgenic rats. Furthermore, Ebert (1988, Mol. Endocrinology, Vol. 2, pages 277-283) taught a transgene encoding the human somatotropin gene operably linked to the mouse metallothionein promoter caused different phenotypes in

transgenic pigs and mice (pg 277, col. 2, lines 17-27).

Transgenic mouse expressing specific type II human phospholipase A_2 with specific phenotype are known in the art (Bennett et al., 1997; US Patent No. 5,625,125), displaying a pathologic phenotype such as adnexal hyperplasia, alopecia, exfoliative dermatitis and hyperkeratosis with increased serum phospholipase A_2 activity.

The claims 1-5, 7-9, 16-17, 37 and 40 of the instant invention are directed to nucleic acids comprised in a vector configured to generate a transgenic mouse overexpressing phospholipase A_2 ($TGiPLA_2$) coding sequence (SEQ ID NO: 6). Phospholipase A_2 genes comprise a family of genes with many sub-groups with varying physical properties and distinct functions (for example search for phospholipase A_2 in Mouse genome Informatics (MGI) site revealed at least 10 sub-groups I-X, said genes widely distributed in various tissues and involved in many different metabolic processes). The art did not teach the function of SEQ ID NO: 6 or the subfamily to which it belongs at the time of the instant invention. Nor does the specification teach the function of SEQ ID NO: 6 with regard to the expected phenotype of transgenic mouse expressing said polypeptide or the subfamily of phospholipases to which it belongs. The specification on pages 57-58, Example 11, describes the generation of transgenic mouse in a vector configured to overexpress phospholipase A_2 ($iPLA_2$). The transgenic mouse showed under fasting conditions the levels of triglycerides were high as compared to the wild-type mouse. In said transgenic mouse under fasting conditions phosphatidylcholine, ethanolamine, glycerphospholipids and plasminogen levels in fed mice were reduced by about 60% of similarly fed wild-type mice (Fig. 26). Triglyceride levels of fed transgenic mice vs. wild-type mice were moderately increased (1.7 fold). Upon fasting in wild-type mice, levels of phosphatidylcholine,

ethanolamine, glycerphospholipids and plasminogen levels were reduced 17% with no significant change in triglyceride levels. In contrast, no significant alterations of phosphatidylcholine, ethanolamine, glycerphospholipids and plasminogen levels were detected upon fasting transgenic mice with 10 fold increase in triglyceride equivalent to a two fold increase in total lipid mass. However, the phenotype described in the specification regarding the generated transgenic mouse does not correlate to any disease condition in humans. The specification does not link SEQ ID NO: 6 to any disease or teach the gene of SEQ ID NO: 6 was overexpressed in any of the patients with disease. Those of skilled in the art would have to test a person with every disease to determine if they overexpressed the polypeptide of SEQ ID NO: 1. The amount of such further investigations is beyond that of normal investigation. More specifically, the amount of investigation required to determine whether every cardiovascular disease or atherosclerotic condition was linked to overexpression of SEQ ID NO: 6 would also be immense. There is no evidence especially any cardiovascular disease or atherosclerotic condition may be linked to overexpression of SEQ ID NO: 6 encoding the polypeptide of SEQ ID NO: 1. Therefore, without sufficient guidance, one skilled in the art would not know how to use the transgenic mice generated by a vector (comprising SEQ ID NO: 6 encoding the polypeptide of SEQ ID NO: 1) configured to generate transgenically generated phospholipase A_2 (TGiPLA_2) mice. The transgenic mice do not have an enabled use as a disease model, therefore, the vector for use in making the transgenic mice does not have an enabled use.

While administering various compounds to the mice generated by the instant invention and observing the change in the triglycerides can be envisioned, the specification does not teach how to identify agents that target the PLA2γ protein using the mouse. Assuming an agent that

decreases triglyceride identified using the mouse does not target phospholipase A_2, the agent could have been found using a wild-type mouse with elevated triglycerides (i.e. put on a high fat or high cholesterol diet) or one of the many other transgenic mice having elevated triglycerides. Elevated triglyceride levels, for example, are generic to 61 different gene disruptions in knockout mice (see MGI webpage labeled "Mammalian Phenotype Ontology Annotations" for increased circulating triglyceride level). Accordingly, using the mouse claimed to identify agents that decrease increased triglyceride levels, does not have an enabled use because i) it cannot be determined how to identify agents that target PLA2γ using the mice of the instant invention, and ii) agents that do not target PLA2γ capable of decreasing triglycerides can be found using a wild-type mouse or any other transgenic showing the same phenotype. The mice made using the constructs claimed are capable of providing data, but they may not reveal the function of the gene. For example, applicants used the mice of the invention in phenotypic analyses without determining the function of the PLA2γ gene, correlating the phenotype to a disease or identifying agents that target PLA2γ. Undue research would be required to identify whether PLA2γ disruptions were linked to elevated triglycerides in humans, to determine the function of the PLA2γ gene, or to determine how to use the mouse to identify agents capable of targeting PLA2γ. The transgenic mice do not have an enabled use to identify compounds that target PLA2γ; therefore, the vector for use in making the transgenic mice does not have an enabled use.

While scientists may have used transgenic mice for basic research at the time of filing, applicants have not set forth the blaze marks for one of skill to conduct any further research so that one of skill would reasonably expect to determine the role of PLA2γ in triglyceride levels or heart disease using the transgenic mice made with the construct claimed.

The specification fails to adequately teach how to make a transgenic mouse using a construct comprising anti-sense sequence of SEQ ID NO: 6 (claim 9). The art doesn't teach how to use anti-sense to make the transgenic mice. The specification does not teach how to make a transgenic mouse using a construct comprising anti-sense sequence of SEQ ID NO: 6. Without such guidance it would have required those of skill undue experimentation to determine how to use a vector encoding anti-sense to make transgenic mice. Accordingly claim 9 is not enabled.

In addition, claims 1-2, 4-5, 7, 9, 16-17 and 40 are so broad as to encompass to any polynucleotide encoding any phospholipase A2γ or any polynucleotide encoding a phospholipase A2γ wherein the isolated polynucleotide sequence has at least 90% sequence identity to SEQ ID NO: 6 or a polynucleotide comprising any fragment length of SEQ ID NO: 6 and encodes a polypeptide with phospholipase A2γ activity or capable of modulating any undefined enzymic activity or any truncated fragment of said polypeptide or any anti-sense sequence of SEQ ID NO: 6 in a vector configured and intended to generate a transgenic mice, said construct further comprising a reporter gene, host cell intended for overexpressing said polypeptide in a transgenic mice or knocking out the expression of said polypeptide in a transgenic mice. The scope of the claims are not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotides and encoding polypeptides broadly encompassed by the claims. Since the amino acid sequence of a protein encoded by a polynucleotide determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires knowledge and guidance with regard to which amino acids in the protein's sequence and the respective codons in its

polynucleotide, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the encoded proteins' structure relates to its function. However, in this case the disclosure is limited to a polynucleotide with SEQ ID NO: 6 and encoding a polypeptide of SEQ ID NO: 1 having phospholipase A2γ activity, vector, host cell, method of making said polypeptide, but provides no guidance with regard to the making of other variants and mutants or with regard to other uses such as modulating the activity of any undefined enzymic activity. In view of the great breadth of the claims, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by these claims.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is not routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions or deletions.

The specification does not support the broad scope of the claims which encompass all modifications of to any polynucleotide encoding any phospholipase A2γ or any polynucleotide encoding a phospholipase A2γ wherein the isolated polynucleotide sequence has at least 90% sequence identity to SEQ ID NO: 6 or a polynucleotide comprising any fragment length of SEQ ID NO: 6 and encodes a polypeptide with phospholipase A2γ activity or capable of modulating any undefined enzymic activity or any truncated fragment of said polypeptide or any anti-sense sequence of SEQ ID NO: 6 in a vector configured and intended to generate a transgenic mice, said construct further comprising a reporter gene, host cell intended for overexpressing said polypeptide in a transgenic mice or knocking out the expression of said polypeptide in a transgenic mice, because the specification does not establish: (A) regions of the polynucleotide/protein structure which may be modified without affecting the activity of encoded phospholipase A2γ or the property of modulating any target of undefined enzymic activity; (B) the general tolerance of the polypeptide and the polynucleotide encoding phospholipase A2γ to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue or the respective codon in the polynucleotide with an expectation of obtaining the desired biological function; (D) a truncated nucleic acid molecule of any fragment length of SEQ ID NO: 6 and encodes a polypeptide with phospholipase A2γ activity or capable of modulating any undefined enzymic activity and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope

of the claims broadly including polynucleotides with an enormous number of modifications. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of polypeptides having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Applicants' have traversed this rejection with the reasoning, the claimed invention is enabled due to the amendments to claims and newly added subject matter to the specification and any person skilled in the art can make and use the invention without undue experimentation and need only routine experimentation. Applicants' arguments have been considered and found to be non-persuasive for the following reasons.

While methods to produce variants of a known sequence, such as site-specific mutagenesis, random mutagenesis, etc., are well known to the skilled artisan, producing variants capable of phospholipase A2γ activity or any fragment having phospholipase A2γ activity, requires that one of ordinary skill in the art know or be provided with guidance for the selection of which, of the infinite number of variants, have the activity. Without such guidance, one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. For the rejected claims, this would clearly constitute **undue** experimentation. Guo et al., (PNAS, 2004, Vol. 101 (25): 9205-9210) teach that the percentage of random single-substitution mutations, which inactivate a protein, using a protein 3-methyladenine DNA glycosylase as a model, is 34% and that this number is consistent with other studies in other proteins (p 9206, paragraph 4). Guo et al., (*supra*) further show that the

percentage of active mutants for multiple mutations appears to be exponentially related to this by the simple formula $(.66)^X$ X 100% where x is the number of mutations introduced (Table 1). Applying this estimate to the protein recited in the instant application, 90% identity allows up to 78 mutations within the 782 amino acids of SEQ ID NO: 1 and, thus, only $(0.66)^{78}$ X 100% or 8.4×10^{-13} % of random mutants having 90% identity would be active. Current techniques in the art (i.e., high throughput mutagenesis and screening techniques) would potentially allow for finding a reasonable number of active mutants within about a hundred thousand inactive mutants. But finding a few mutants within several million or more (in the instant case several billions), as in the claim to 90% identity or truncated polypeptide, would not be possible. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification.

Applying this estimate to the instant protein, a functional equivalent thereof with 90% sequence identity or a truncated polypeptide with any or no activity or able to modulate any undefined target, as recited in Claims 1-2, 4-5, 7, 9, 16-17, 37 and 40, an extremely low number of active mutants will be present among an enormously large number of inactive mutants and as such screening for these active mutants would be burdensome and undue experimentation when there is no guidance provided in the specification.

Written description

Claims 1-2, 4-5, 7, 9, 16-17 and 40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In response to the above rejection, applicants' have traversed on the basis that: "applicants' have amended the specification to include any isolated nucleic acid including a polynucleotide encoding a phospholipase A2γ and an in vitro expression construct in which any truncated iPLA2γ of any length is cloned downstream from a SV 40 promoter of a vector configured to a generate a transgenic mice..." Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons.

Claims 1-2, 4-5, 7, 9, 16-17 and 40 (as interpreted), are directed to a genus of polynucleotides encoding polypeptides including variants, mutants and recombinants from any source with no support in the specification for the structural details associated with the function i.e., wherein the isolated polynucleotide sequence has at least 90% sequence identity to SEQ ID NO: 6 or any polynucleotide comprising any fragment length of SEQ ID NO: 6 and encodes a polypeptide with phospholipase A2γ activity or capable of modulating any undefined enzymic activity or any truncated fragment of said polypeptide or any anti-sense sequence of SEQ ID NO: 6 in a vector configured and intended to generate a transgenic mice, said construct further comprising a reporter gene, host cell intended for overexpressing said polypeptide in a transgenic mice or knocking out the expression of said polypeptide in a transgenic mice. While the specification discloses the structure and characterization of the isolation of a polynucleotide with SEQ ID NO: 6 and encoding a polypeptide of SEQ ID NO: 1 having phospholipase A2γ activity, vector, host cell, method of making said polypeptide, the specification is silent in regard to (1) the structures and functions of all the polynucleotides and encoding polypeptides encompassed

by the claims, (2) the critical structural elements of any variants, mutants, recombinants and truncated polypeptides having phospholipase A2γ activity from any source (3) the targets that are being modulated by said polypeptides and the type of modulation and (4) the intended phenotype of the transgenic mice by the use of the vector comprising said polynucleotides configured to generate a transgenic mice.

The genus of polynucleotides and encoding polypeptides required in the claimed invention is an extremely large structurally variable genus. While the argument can be made that the recited genus of polynucleotides and encoding polypeptides are adequately described by the disclosure of the structure of the of a polynucleotide with SEQ ID NO: 6 and encoding a polypeptide of SEQ ID NO: 1 having phospholipase A2γ activity, since one could use structural homology to isolate those polynucleotides and encoding polypeptides recited in the claims, as taught by the art. Even highly structurally homologous polypeptides do not necessarily share the same function. For example, Witkowski et al. (Biochemistry 38:11643-11650, 1999), teaches that one conservative amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Seffernick et al. (J. Bacteriol. 183(8): 2405-2410, 2001), teaches that two naturally occurring *Pseudomonas* enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al. (Science 282:1315-1317, 1998), teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. Furthermore, the targets that are being modulated by said polypeptides and the intended phenotype of transgenic mice expressing said polypeptides is completely undefined. Therefore,

the claimed genera of polynucleotides and encoding polypeptides include proteins having widely variable structures, since minor changes may result in changes affecting function and no additional information correlating structure with function has been provided.

Many structurally unrelated polynucleotides and encoding polypeptides are encompassed by these claims. The specification only discloses a single species of the recited genus, the specification is silent regarding the targets that are modulated by said encoded polypeptides and the phenotype of transgenic mice expressing said polypeptide or the phenotype of the gene knockout mice wherein the expression of the polypeptide is eliminated. The disclosure is insufficient to put one of ordinary skill in the art in possession of all attributes and features of all species within the required genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Applicants are referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

New-Claim Rejections 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 4-5 and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by Bennett et al., (US Patent 5,625,125) when given the broadest interpretation. Claims 1-2, 4-5 and

40 are directed to any isolated polynucleotide encoding any phospholipase A2γ configured to generate transgenically generated phospholipase A2 mice, said phospholipase A2 catalyzes cleavage of fatty acid from sn-2 position of phospholipids, vector comprising said nucleic acid molecule and a cell transformed or transfected with said vector or an expression construct with a truncated version of phospholipase A2.

Bennett et al., (*supra)* disclose a vector comprising the isolated polynucleotide encoding the phospholipase A2 enzyme/polypeptide, the truncated version of the polypeptide and the use of the said vector in the generation of transgenic mice and rat expressing said polypeptides. Therefore the reference of Bennett et al., anticipates the claims 1-2, 4-5 and 40.

Maintained-Claim Rejections 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-5, 7, 9 and 40 are rejected under 35 U.S.C. 102(a) as being anticipated by Tanaka et al., (Biochem. Biophysical Res. Commun., 2000, Vol. 272: 320-326, published June 07, 2000). Claims 1-5, 7-9 and 40, are directed to an isolated nucleic acid molecule comprising the polynucleotide encoding a phospholipase A2γ polypeptide of SEQ ID NO: 1, vector, isolated host cell, said polynucleotide comprises the nucleotide sequence of SEQ ID NO: 6 or having about 90% sequence identity to SEQ ID NO: 6 and an in vitro expression construct in which a truncated nucleic acid molecule of SEQ ID NO: 6 is cloned into an expression vector. Tanaka et al., (*supra*) teach the isolation of a polynucleotide from human that has 90.8% homology to SEQ

ID NO: 6 of the instant application and encoding a polypeptide having phospholipase A2γ activity that has 100% homology to SEQ ID NO: 1 of the instant application (see sequence alignment provided). Furthermore, the reference also teaches the recombinant expression constructs (expression vector pEF-BOS-FF driven by SV 40 promoter), host cells and method of making said polypeptide including isolation of truncated EST clones of said polynucleotide (Materials and Methods, page 320 and Results and Discussion, pages 321-324) and therefore, Tanaka et al., anticipate claims 1-5, 7, 9 and 40 as written.

Applicants' have traversed the rejections with the argument that Tanaka et al., do not describe a vector comprising SEQ ID NO: 6 encoding the polypeptide of SEQ ID NO: 1 configured to transgenically generated phospholipase A2 ($TGiPLA_2$) mice. Applicants' arguments have been considered and found to be non-persuasive, because any vector can be configured to generate transgenically generated phospholipase A2 ($TGiPLA_2$) mice as now claimed. The phrase does not distinguish the function or structure of the vector claimed over the vector described by Tanaka et al., because any vector can be configured to generate transgenically generated phospholipase A2 ($TGiPLA_2$) mice.

Claims 1-5, 7, 9 and 40 are rejected under 35 U.S.C. 102(a) as being anticipated by Mancuso et al., (JBC., 2000, Vol. 275 (14): 9937-9945, published April 07, 2000). Claims 1-5, 7-9 and 40, are directed to an isolated nucleic acid molecule comprising the polynucleotide encoding a phospholipase A2γ polypeptide of SEQ ID NO: 1, vector, isolated host cell, said polynucleotide comprises the nucleotide sequence of SEQ ID NO: 6 or having about 90% sequence identity to SEQ ID NO: 6 and an in vitro expression construct in which a truncated nucleic acid molecule of SEQ ID NO: 6 is cloned into an expression vector. Mancuso et al.,

(*supra*) teach the isolation of a polynucleotide from human that has 100% homology to SEQ ID NO: 6 of the instant application and encoding a polypeptide having phospholipase A2γ activity that has 100% homology to SEQ ID NO: 1 of the instant application (see sequence alignment provided). Furthermore, the reference also teaches the recombinant expression constructs (expression vector pFASTBAC driven by SV 40 promoter), host cells and method of making said polypeptide including isolation of truncated EST clones of said polynucleotide (Fig. 1 and Results section, page 9939) and therefore, Mancuso et al., anticipate claims 1-5, 7, 9 and 40 as written.

Applicants' have traversed the rejections with the argument that Mancuso et al., do not describe a vector comprising SEQ ID NO: 6 encoding the polypeptide of SEQ ID NO: 1 configured to transgenically generated phospholipase A2 ($TGiPLA_2$) mice. Applicants' arguments have been considered and found to be non-persuasive, because any vector can be configured to generate transgenically generated phospholipase A2 ($TGiPLA_2$) mice as now claimed. The phrase does not distinguish the function or structure of the vector claimed over the vector described by Mancuso et al., because any vector can be configured to generate transgenically generated phospholipase A2 ($TGiPLA_2$) mice.

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 9 is rejected under 35 U.S.C. 102(e) as being anticipated by Tang et al., (US 6,569,662 B1, publication date May 27, 2003 claiming the priority date of Application No.: 09/488,725 filed on Jan. 21, 2000). Claim 9 is directed to an anti-sense sequence, which

specifically hybridizes to SEQ ID NO: 6, wherein the antisense sequence is configured to generate transgenically generated phospholipase A2 ($TGiPLA_2$) mice.

Applicants' have traversed the rejections with the argument that Tang et al., do not describe a vector comprising an anti-sense sequence of SEQ ID NO: 6, wherein the anti-sense configured to transgenically generated phospholipase A2 ($TGiPLA_2$) mice. Applicants' arguments have been considered and found to be non-persuasive, because any vector can be configured to generate transgenically generated phospholipase A2 ($TGiPLA_2$) mice as now claimed. The phrase does not distinguish the function or structure of the vector claimed over the vector described by Tang et al., because any vector can be configured to comprise an anti-sense sequence of SEQ ID NO: 6 to generate transgenically generated phospholipase A2 ($TGiPLA_2$) mice.

Claim 9 is rejected under 35 U.S.C. 102(e) as being anticipated by Yue et al., (US PGPUB No.: US 2004/0248243 A1, publication date Dec. 09, 2004 claiming the priority date of Provisional Application No.: 60/177,732 filed on Jan. 21, 2000). Claim 9 is directed to an anti-sense sequence, which specifically hybridizes to SEQ ID NO: 6, wherein the antisense sequence is configured to generate transgenically generated phospholipase A2 ($TGiPLA_2$) mice.

Applicants' have traversed the rejections with the argument that Yue et al., do not describe a vector comprising an anti-sense sequence of SEQ ID NO: 6, wherein the anti-sense configured to transgenically generated phospholipase A2 ($TGiPLA_2$) mice. Applicants' arguments have been considered and found to be non-persuasive, because any vector can be configured to generate transgenically generated phospholipase A2 ($TGiPLA_2$) mice as now claimed. The phrase does not distinguish the function of the vector claimed over the vector

described by Yue et al., because any vector can be configured to comprise an anti-sense sequence of SEQ ID NO: 6 to generate transgenically generated phospholipase A2 ($TGiPLA_2$) mice.

Withdrawn- Claim Rejections: 35 USC § 103

In view of applicants' amendment, the previous rejection of claims 1-5, 7-9, 16-17, 37 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tanaka et al., (Biochem. 2000) or Mancuso et al., (2000) and further in view of McTiernan et al., (1999) is withdrawn.

New-Claim Rejections 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 7, 8 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bennett et al., (US Patent 5,625,125) in view of Tanaka et al., (published June 07, 2000) or Mancuso et al., (published April 07, 2000). Bennett et al., (*supra)* disclose the construction of a transgenic vector comprising the isolated polynucleotide encoding the phospholipase A2 enzyme/polypeptide, the truncated version of the said gene encoding the polypeptide and the use of the said vector in the generation of transgenic mice and rat expressing said polypeptides. Bennett et al., does not specifically teach the vector comprised SEQ ID NO: 6, wherein the encoded polypeptide with phospholipase A2γ activity has/modulates enzymatic activity. Tanaka et al., or Mancuso et al., (*supra*) teach the molecular cloning and characterization of a polynucleotide from human origin that has 100% sequence homology to SEQ ID NO: 6 and

encoding a polypeptide having phospholipase A2γ activity that has 100% sequence homology to SEQ ID NO: 1 of the instant application (see sequence alignment provided). It would have been obvious to a person of ordinary skill in the art to make a vector encoding phospholipase A2γ operably linked to the SV40 promoter for use in transgenic mouse as taught by Bennett et al., wherein the phospholipase A2γ polynucleotide sequence was SEQ ID NO: 6 taught by Tanaka et al., or Mancuso et al.,. Those of ordinary skill in the art at the time of invention was made would have been motivated to make the phospholipase A2γ construct taught by Bennett et al., using the sequence phospholipase A2γ of SEQ ID NO: 6 of Tanaka et al., or Mancuso et al., to determine the function of phospholipase A2γ *in vivo*. Those of ordinary skill would have recognized that the transgenics could be used to identify compounds that modulate phospholipase A2γ activity. The expectation of success of merely making the vector is high, because methods for constructing transgenic vectors configured to express phospholipase in a transgenic mouse were well known in the art as supported by Bennett et al.,.

Claims 1-5, 7-8, 16-17, 37 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Bennett et al., (US Patent 5,625,125) and Tanaka et al., (published June 07, 2000) or Mancuso et al., (published April 07, 2000) and further in view of McTiernan et al., (US Patent No.: 5,917,123). The combination of Bennett et al., and Tanaka et al., or Mancuso et al., teaches a vector encoding phospholipase A2γ of SEQ ID NO: 6 operably linked to the SV40 promoter for use in transgenic mice. Said combination does not teach the vector for use in transgenic mice further comprising a reporter gene encoding luciferase or a promoter controlling the expression of desired gene for myocardial specific expression. McTiernan et al., (*supra*) teach transgenic vector constructs comprising different MHC

promoters driving the gene of interest including the reporter gene luciferase, specifically for expression of gene of interest in cardiac tissues and also method for generating a transgenic mouse with said constructs (entire document). It would have been obvious to a person of ordinary skill in the art to combine the teachings of Bennett et al., Tanaka et al., Mancuso and McTiernan et al., to produce a transgenic vector comprising the polynucleotide of Tanaka et al., or Mancuso et al., of SEQ ID NO: 6 linked to the a reporter gene encoding luiciferase and a promoter controlling the expression of desired gene for myocardial specific expression of McTiernan et al.,. Motivation to do so derives from the fact that the vector design of McTiernan et al., et al., would result in efficient expression of gene of interest in target tissues such as cardiac tissues and to understand the pathological effects of overexpression of phospholipases in cardiac tissue as phospholipase A2 activity is implicated in the pathophysiology of cardiac tissue i. e., atherosclerosis (Bennett et al., column 6, lines 63-65). Such a transgenic mouse would also serve as animal model to test the inhibitors of phospholipases. The expectation of success is high, because methods for constructing transgenic vectors configured to express phospholipase in a transgenic mice were well known in the art and Bennett et al., Tanaka et al., Mancuso et al., and McTiernan et al., teach the methods and structural elements for making such a vector configured to generate a transgenic mice expressing phospholipase A2 ($TGiPLA_2$) mice and to express the phospholipase A2 in clinically significant tissues such as cardiac tissue.

The above references render claims 1-5, 7-8, 16-17, 37 and 40 *prima facie* obvious to one of ordinary skill in the art.

Applicants' have amended the claims and have argued that with the amendments none of the cited references render claims 1-5, 7, 8, 16-17, 37 and 40 obvious over prior cited references.

Applicants' arguments have been fully considered but are not deemed persuasive as the cited references indeed render the instant invention obvious over cited prior art, as the references provide the structural elements, method for constructing vectors for generation of transgenic mice, motivation and expectation of success.

Summary of Pending Issues

The following is a summary of issues pending in the instant application.

1. Amended claims 1, 7, 9, 37 and 40 are objected to, due to informalities.

2. Claims 1-5, 7-8, 16-17, 37 and 40 are rejected under 35 U.S.C. 112, second paragraph.

3. Claims 1-5, 7-9, 16-17, 37 and 40 are rejected for failing to comply with 35 U.S.C. 112 first paragraph for enablement and written description.

4. Claims 1-2, 4-5 and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by Bennett et al., (US Patent 5,625,125).

5. Claims 1-5, 7, 9 and 40 are rejected under 35 U.S.C. 102(a) as being anticipated by Tanaka et al., (Biochem. Biophysical Res. Commun., 2000, Vol. 272: 320-326, published June 07, 2000) and Claims 1-5, 7, 9 and 40 are rejected under 35 U.S.C. 102(a) as being anticipated by Mancuso et al., (JBC., 2000, Vol. 275 (14): 9937-9945, published April 07, 2000).

6. Claim 9 is rejected under 35 U.S.C. 102(e) as being anticipated by Tang et al., (US 6,569,662 B1) and Yue et al., (US PGPUB No.: US 2004/0248243 A1).

7. Claims 1-5, 7, 8, 16-17, 37 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Bennett et al., (US Patent 5,625,125), Tanaka et al.,

(published June 07, 2000) or Mancuso et al., (published April 07, 2000) and in further view of McTiernan et al., (US Patent No.: 5,917,123).

Allowable Subject Matter/Conclusion

None of the claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathirama Raghu whose telephone number is 571-272-4533. The examiner can normally be reached on M-F; 8:00-4:30 pm EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of the application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ganapathirama Raghu, Ph.D.
Patent Examiner
Art Unit 1652
April 07, 2007.